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[Continued on next page]

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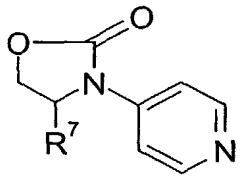
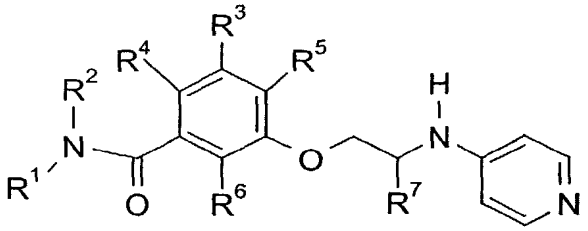


(II)



(I)

(57) Abstract: A novel intermediate of formula (II) is provided for use in an improved process for the preparation of benzamide derivatives of formula (I) which are known to be thrombin inhibitors, wherein: R^1 and R^2 independently represent a group (VII) or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group; R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy; R^4, R^5 and R^6 independently represent hydrogen, or halogen; R^7 represents hydrogen or C_{1-6}alkyl; R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, $CO_2R^{14}CONR^{15}R^{16}$, and SO_2NHR^{17}; X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$ and SO_2NHR^{17}; R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7}heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl.

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PROCESSES FOR THE MANUFACTURE OF THROMBIN INHIBITORS AND N-PYRIDIN-4-YL-OXAZOLIDIN-2-ONES AS INTERMEDIATE THEREFOR

Field of the Invention

The present invention relates to a novel intermediate which can be used in an improved process for the preparation of certain benzamide derivatives known to be useful as thrombin inhibitors.

Background of the Invention

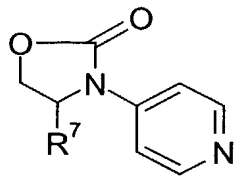
Thrombin is a serine proteinase present in plasma and is formed by conversion from its prothrombin precursor by the action of Factor Xa. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. Thrombin inhibitors have been described as being useful in the treatment of acute vascular diseases such as coronary thrombosis, stroke, pulmonary embolism, deep vein thrombosis, restenosis, atrial fibrillation, myocardial infarction, and unstable angina. They have been described as anti-coagulant agents both in-vivo and ex-vivo, and in oedema and inflammation, whereby a low dose of thrombin inhibitor can reduce platelet and endothelial cell thrombin mediated inflammatory responses without concomitant anticoagulant effects. Thrombin has been reported to contribute to lung fibroblast proliferation, thus, thrombin inhibitors could be useful for the treatment of some pulmonary fibrotic diseases. Thrombin inhibitors have also been reported in the treatment of tumour metastasis. Further potential uses include the treatment of neurogenerative diseases such as Parkinson's and Alzheimer's disease, the treatment of Kasabach Merritt Syndrome and haemolytic uremic syndrome (US5371091), the prevention of fibrin deposits in the eye during ophthalmic surgery (EP565897), and in the treatment of osteoporosis (DE4126277).

Thrombin inhibitors and processes for their preparation have been previously described in WO97/22589 (Glaxo Group Limited) and WO00/20394 (Glaxo Group Limited).

Summary of the Invention

The present inventors have found a novel intermediate, an oxazolidinone, that can be used in an improved process for preparing benzamide derivatives. The improved process is more direct, provides increased yield and avoids the use of potential alkylating intermediates compared to the previous processes such as those described in WO97/22589 & WO00/20394.

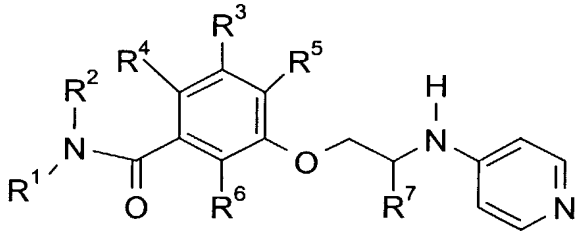
Accordingly, the present invention provides a compound of formula (II):



(II)

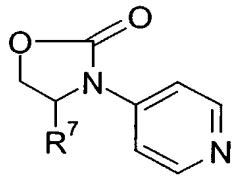
wherein R^7 represents hydrogen or C_{1-6}alkyl;
or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

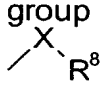
comprising the step of preparing a compound of formula (II) or a pharmaceutically acceptable salt or solvate thereof:



(II)

wherein:

R^1 and R^2 independently represent a group



or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

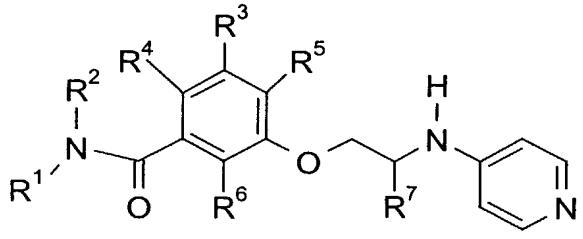
R^7 represents hydrogen or C_{1-6}alkyl;

R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

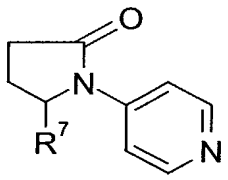
R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl.

In an alternative aspect, the invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:

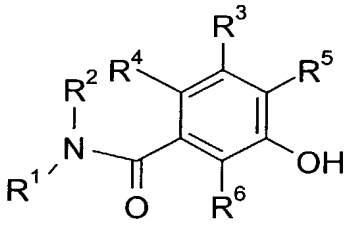


(I)

comprising the step of reacting a compound of formula (II) with a compound of formula (III):



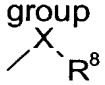
(II)



(III)

wherein:

R^1 and R^2 independently represent a group



or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

R^7 represents hydrogen or C_{1-6}alkyl;

R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl.

Detailed Description of the Invention

As used herein, the terms "alkyl" and "alkoxy" mean both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl (-CH_3), ethyl (-C_2H_5), propyl (-C_3H_7) and butyl (-C_4H_9). Examples of alkoxy groups include methoxy (-OCH_3) and ethoxy (-OC_2H_5).

As used herein, the term "alkenyl" means both straight and branched chain unsaturated hydrocarbon groups. Examples of alkenyl groups include ethylene (-$CH=CH_2$) and propylene (-$CH=CHCH_3$ or –$CH_2CH=CH_2$).

As used herein, the term "halogen" means fluorine, chlorine, bromine and iodine.

As used herein, the term "cycloalkyl group" means an aliphatic ring. Examples of cycloalkyl groups include cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "cycloalkenyl" means an aliphatic ring containing at least one double bond incorporated in the ring.

As used herein, the term "heterocycloalkyl" means an aliphatic ring containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, for example, pyrrolidine, morpholine or a tetrahydropyran-4-yl group.

As used herein, the term "heterocycloalkenyl" means an aliphatic ring containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, together with at least one double bond incorporated in the ring.

As used herein, the term "aryl" means optionally substituted monocyclic or bicyclic aromatic carbocyclic groups such as phenyl and naphthyl.

As used herein, the term "heteroaryl" includes 5 or 6 membered aromatic heterocyclic rings containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, and fused bicyclic ring systems containing one or more nitrogen, sulfur, and oxygen atoms. Examples of such groups include oxadiazole, thiazole, thiadiazole, triazole, tetrazole, benzimidazole, pyridine, furan and thiophene.

Referring to the general formula (I) where R^1 represents a group

X is suitably a bond or C_{1-6}alkyl group, e.g. methyl, isopropyl or isobutyl, and R^8 suitably represents hydrogen, C_{3-8}cycloalkyl, aryl, or heteroaryl. When X represents a bond, R^8 is preferably phenyl optionally substituted by one or more halogen groups, or C_{3-8}cycloalkyl, e.g. cyclobutyl, cyclopentyl or cyclohexyl. When X represents a C_{1-6}alkyl group, R^8 is preferably hydrogen, cycloalkyl, e.g. cyclohexyl, or heteroaryl, e.g. thienyl or furyl. More preferably, R^1 represents propyl, isopropyl, butyl, cyclopentyl or cyclohexyl. Most preferably R^1 represents isopropyl.

Referring to the general formula (I) where R^2 represents a group

X is suitably C_{3-6}alkenyl, e.g. allyl, or C_{1-6}alkyl, e.g. methyl, ethyl, propyl or pentyl, which optionally contains an oxygen group within the chain and is optionally substituted by a group selected from hydroxy, C_{1-6}alkoxy, $NHSO_2R^{12}$, CO_2R^{14}, $CONR^{15}R^{16}$, or SO_2NHR^{17}, and R^8 is suitably hydrogen, C_{3-7} heterocycloalkyl, e.g. pyrrolidine or morpholine, aryl, e.g. phenyl which is optionally substituted by CO_2R^{14}, or heteroaryl, e.g. oxadiazole optionally substituted by hydroxy, triazole, or tetrazole optionally substituted by C_{1-6}alkyl. More preferably, R^2 represents methyl, ethyl, propyl or isopropyl. Most preferably R^2 represents ethyl.

R^3 is preferably C_{1-3}alkyl, e.g. methyl, or halogen, e.g. chlorine or bromine. More preferably, R^3 represents methyl or chlorine. Most preferably, R^3 represents methyl.

R^4, R^5 and R^6 are preferably hydrogen, or halogen, e.g. fluorine. More preferably R^4, R^5 and R^6 represent hydrogen.

R^7 is preferably hydrogen, methyl or ethyl. More preferably R^7 is methyl.

Particularly preferred compounds, or compounds of the processes of the invention, include those in which each variable is selected from the preferred groups for each variable. Even more preferable compounds, or compounds of the processes of the invention, include those in which each variable is selected from the more preferred or most preferred groups for each variable.

In a particularly preferred aspect of the invention R^1 represents C_{1-4}alkyl or C_{3-7}cycloalkyl;
R^2 represents C_{1-4}alkyl or C_{3-4}alkenyl;
R^3 represents hydrogen, C_{1-3}alkyl or halogen;
R^4 represents hydrogen;
R^5 represents hydrogen;
R^6 represents hydrogen;
R^7 represents hydrogen or C_{1-6}alkyl.

Preferably the compound of formula (I) is N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated that the compounds of formula (I) are optically active. Processes for preparing individual, isolated isomers and mixtures thereof, including racemates, are within the scope of the present invention.

As used herein the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, di-p-toluoyl tartrate, sulfanilic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Preferred pharmaceutically acceptable salts of the compounds of formula (I) include the toluene-p-sulphonic acid salt. Other acids such as oxalic, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

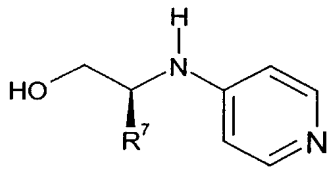
Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I) are within the scope of the invention.

Preferably, reaction of a compound of formula (II) with a compound of formula (III) is carried out in the presence of an organic solvent, preferably a dipolar organic solvent, e.g. N,N-dimethylformamide (DMF), N-methyl pyrrolidone (NMP), preferably NMP, and a suitable base, e.g. Cs_2CO_3 or K_2CO_3, preferably Cs_2CO_3. The reaction is suitably carried out at elevated temperature, preferably at about 110-120°C. Optionally, the compound of formula (I) may be converted

into a pharmaceutically acceptable salt. For example, a tosylate salt of a compound of formula (I) may be prepared by treatment with p-toluene sulphonic acid monohydrate (pTSA.H_2O). Suitably the conversion is carried out at room temperature or elevated temperature, preferably elevated temperature, more preferably at about 55-70°C in a suitable solvent, eg ethyl acetate/IMS, isopropyl acetate/isopropylalcohol or methylisobutylketone (MIBK), preferably MIBK.

In the following description, the R groups are as defined above unless otherwise stated.

A compound of formula (II) may be prepared by cyclisation of a compound of formula (IV):



(IV)

Suitably, the reaction is carried out in the presence of a dipolar aprotic solvent, e.g. DMF, DMSO or N-methyl pyrrolidone (NMP), preferably NMP; carbonyl equivalents, e.g. diethyl carbonate ($(EtO)_2CO$), phosgene, ethyl chloroform, preferably diethyl carbonate; and a base, e.g. Cs_2CO_3 or K_2CO_3, preferably Cs_2CO_3. Suitably, the reaction is carried out at elevated temperature. Preferably, the reaction is carried out in the presence of NMP, diethyl carbonate and Cs_2CO_3 at a temperature of about 90-125°C.

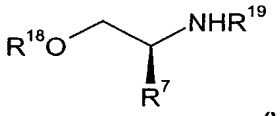
Hence, in a further aspect the present invention provides a process for preparing a compound of formula (I) comprising the step of preparing a compound of formula (II) wherein the compound of formula (II) is prepared by cyclisation of a compound of formula (IV).

The conversion of a compound of formula (IV) to a compound of formula (II) and subsequent reaction of a compound of formula (II) with a compound of formula

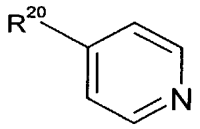
(III) to form a compound of formula (I) may be carried out separately or in situ. The reaction is preferably carried out in situ.

A compound of formula (IV) may be prepared according to processes described in the art, e.g. WO97/22589, WO 00/20394.

Alternatively, a compound of formula (IV) may be prepared by reacting a compound of formula (V) with a compound of formula (VI):



(V)



(VI)

wherein:
R^{18} represents hydrogen, or a suitable oxygen protecting group, preferably R^{18} represents hydrogen.
R^{19} represents hydrogen, or a suitable amino protecting group, preferably R^{19} represents hydrogen; and
R^{20} represents halogen, preferably R^{20} represents chlorine.

Suitably, the compound of formula (VI) is an acid salt, e.g. acetate, HCl or HBr, preferably, an HCl salt. The reaction is suitably carried out at a temperature greater than or equal to about 110°C, preferably, at about 120-140°C. Preferably, the reaction is carried out in the presence of a solvent selected from 2-methoxyethanol, 2-ethoxyethanol, propan-1-ol or ethyleneglycol, preferably 2-ethoxyethanol or propan-1-ol.The reaction may be quenched using an aqueous solution of an inorganic base, e.g. LiOH, NaOH, preferably, NaOH.

Preferably, the compound of formula (IV) is (S)-2-(Pyridin-4-ylamino)-propan-1-ol.

Hence, a further aspect of the present invention is a process for preparing a compound of formula (I) comprising the step of preparing a compound of formula (IV) by reacting a compound of formula (V) with a compound of formula (VI).

Compounds of formulae (III), (V) and (VI) are known compounds and can be prepared by processes well known in the art, for example, as described in WO97/22589 and WO00/20394.

Those skilled in the art will appreciate that in the preparation of the compound of formula (I) or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. The protecting groups used in the preparation of the compound of formula (I) may be used in a conventional manner. See for example Protective Groups in Organic Chemistry, Ed. J.F.W. McOmie, Plenum Press, London (1973) or Protective Groups in Organic Synthesis, Theodora Green, John Wiley and Sons, New York (1981). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate. Examples of suitable amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Removal of any protecting groups present may be achieved by conventional procedures. An arylalkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst, e.g., palladium on charcoal; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation.

As will be appreciated, in any of the general processes described above it may be desirable or even necessary to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes.

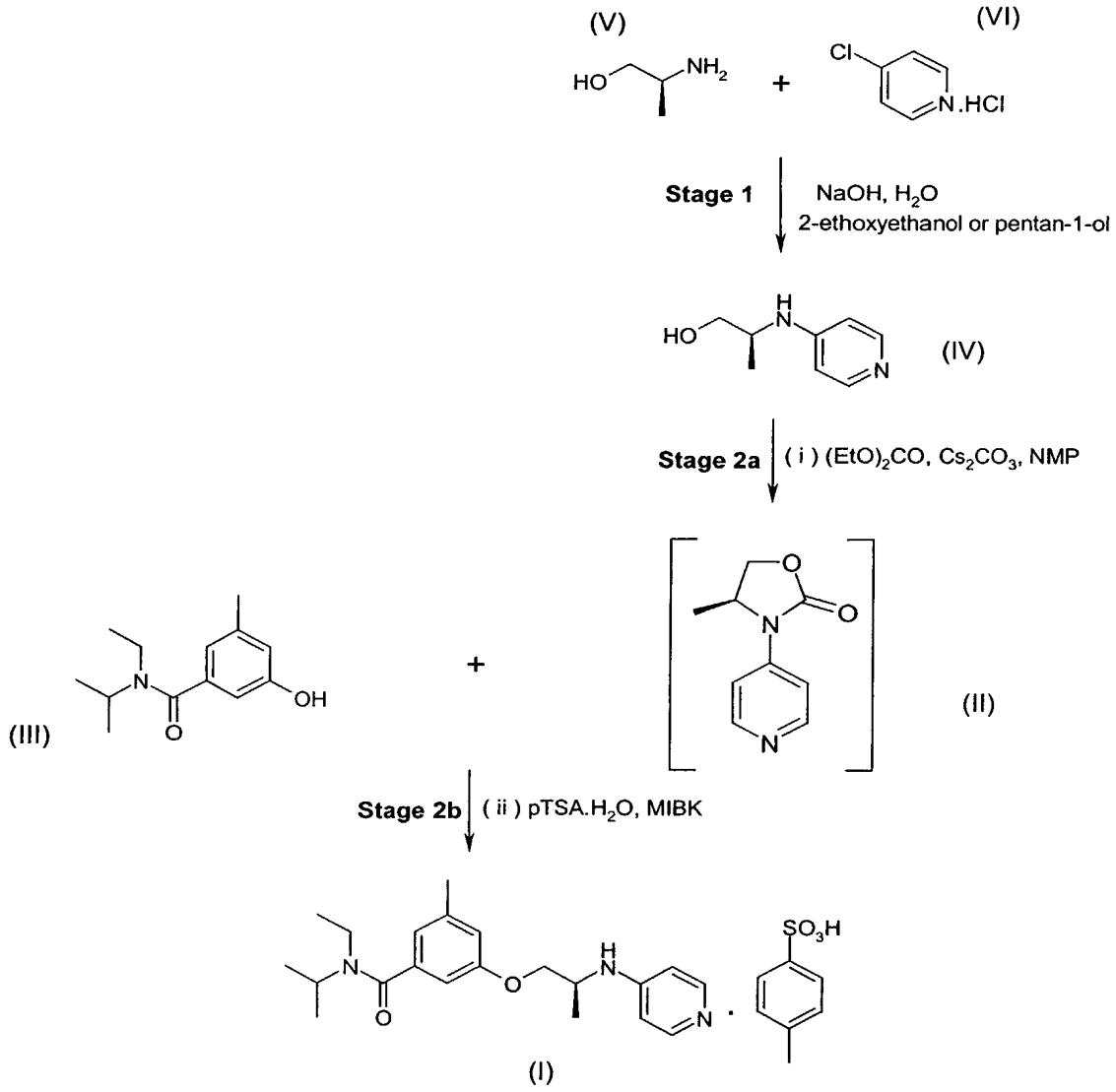
Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the general processes:

(i) removal of any protecting groups; and

(ii) conversion of a compound of formula (I) or a solvate thereof into a pharmaceutically acceptable solvate thereof.

The following examples illustrate aspects of this invention but should not be construed as limiting the scope of the invention in any way.

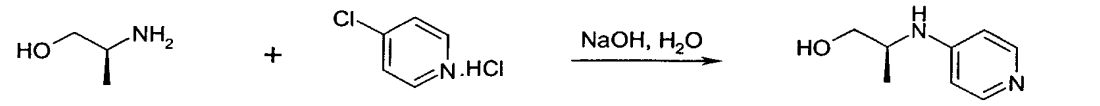
Examples:


(V)
(VI)
HO
NH2
Cl
N.HCl
Stage 1
NaOH, H2O
2-ethoxyethanol or pentan-1-ol
HO
H
N
N
(IV)
Stage 2a
(i) (EtO)2CO, Cs2CO3, NMP
O
N
O
N
(III)
N
OH
O
+
(II)
Stage 2b
(ii) pTSA.H2O, MIBK
N
O
O
H
N
N
SO3H
(I)

5

Stage 1

Intermediate 1: Preparation of (S)-2-(Pyridin-4-ylamino)-propan-1-ol



(S)-(+)-2-amino-1-propanol (V) | 4-chloropyridine.HCl (VI) | (S)-2-(pyridin-4-yl)-propan-1-ol (IV)

(i) Method 1

4-chloropyridine hydrochloride (1 wt, 1 mole equiv) was added to (S)-(+)-2-amino-1-propanol (1 wt, 2 mole equiv) with stirring. The resulting oil was heated at 125°C ± 5°C for 40h. The reaction mixture was then cooled to 105°C and water was added (1-2 vol). 4M NaOH solution (3.3 vol, 2 mole equiv) was added[1] and the mixture was cooled to ambient temperature[2]. The resulting slurry was cooled to 10-15°C and then filtered. The solids were then washed (with thorough slurrying) with 2 x 2 vol water & then dried under vacuum at 50°C.

Typical yield = 70-75%th

[1]A thick precipitate was formed during the NaOH addition.

[2] Brine (NaCl) may be added to 'salt' out further product

(ii) Method 2

4-chloropyridne hydrochloride (1wt, 1eq) is added portion-wise to (L)-alaninol (1wt, 2 eq) to give an amber coloured solution which is then stirred until the contents temperature falls below 30°C ± 5 °C. 2-ethoxyethanol (2vol.) is then added and the resulting solution is warmed to 135°C ± 5 °C and maintained at this temperature for at least 40hours.

2-ethoxyethanol is then removed by distillation & the contents temperature is then adjusted to 90°C ± 5°C. Water (3 vol) is added to the residue and the resulting solution is cooled to 75°C ±5°C.

32% w/w sodium hydroxide solution (1.75 wt) is added, maintaining a contents temperature of 75°C ± 5°C. The resulting suspension is cooled to 20°C ±5°C over a period of 2-4h & aged for a minimum of a further 2h before being filtered and washed with water (2 x 2vol).The solid is collected and dried under vacuum.

Typical yield = 70-75%th

Stages 2a and 2b

Example 1: Preparation of N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (tosylate salt)

(i) Method 1

(S)-2-(Pyridin-4-ylamino)-propan-1-ol (1.0 eq, 1wt) (Intermediate 1 prepared as described above or as described in WO97/22589 and WO00/20394), caesium carbonate (0.1 eq.) and diethyl carbonate (1.1 eq.) were stirred together in N,N-dimethylformamide (5vol.) in a CLR. The mixture was heated, with stirring, to a temperature of about 90°C. The mixture was then heated at this temperature for at least 1 hour. N-ethyl-3-hydroxy-N-isopropyl-5-methylbenzamide (1.1 eq.) and further caesium carbonate (1.4 eq.) were charged to the reaction mixture and the temperature raised to approx. 110-120°C.

Water (6vol.) was added to the mixture, which was then cooled and extracted into toluene (2 x 5vol). The organic extract was washed with 2M sodium hydroxide solution (5vol.) and demineralised water then evaporated under reduced pressure to afford N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide as a brown viscous oil.

N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (1.0 eq., 1.0 wt) was dissolved in ethyl acetate/IMS (15 vol., 60:1 ratio), the resultant solution was then warmed to approx. 70°C. p-toluene sulphonic acid monohydrate (1.1 eq.) was added and stirred at approx. 70°C, the resultant solution was then cooled to approx. 30-40°C. Authentic N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (tosylate salt) was then introduced as a seed and the solution is aged below 25°C. The solid was isolated by filtration, may be washed with EtOAc (2 x 2vol.) & then dried *in vacuo* at 45-55°C.

Typical yield 70-75%th

^{1}H NMR (DMSO-d_6, 500 MHz) ppm 13.12 (s, 1H, 1NH$^+$), 8.64 (d, 1H, 7NH), 8.23 (d, 1H, 2), 8.09 (d, 1H, 6), 7.51 (d, 2H, 29,31), 7.11 (d, 2H, 28,32), 7.04 (dd, 1H, 3), 6.90 (dd, 1H, 5), 6.78 (s, 1H, 13), 6.68 (s, 1H, 15), 6.61 (s, 1H, 17), 4.39 (bs, -, rotamer of 21), 4.22 (m, 1H, 8), 4.08 (dd, 1H, 10), 3.98 (dd, 1H, 10'), 3.76 (bs, 1H,

21), 3.38 (s, -, water), 3.28,3.12(2bs, 2H, 24), 2.50 (p, -, dmso-d_5), 2.28, 2.27 (2s, 6H, 18,26), 1.33-0.84 (bm, 9H, 22,23,25), 1.27 (d, 3H, 9).

(ii) Method 2

(S)-2-(Pyridin-4-ylamino)-propan-1-ol (1.0 eq, 1wt) (Intermediate 1 prepared as described above or as described in WO97/22589 and WO00/20394), caesium carbonate (2.1 eq.) and N-ethyl-3-hydroxy-N-isopropyl-5-methylbenzamide (1.1 eq.) were stirred together in N,N-dimethylformamide (5vol.) in a CLR at 90°C. Diethyl carbonate (1.1 eq.) was added dropwise, the mixture warmed to 110-120°C and then heated at this temperature for at least 15 hours. Water (6vol.) was added to the mixture, which was then cooled and extracted into ethyl acetate (2 x 5vol). The organic extract was washed with 2M sodium hydroxide solution (5vol.). The organic extract was dried by azeotropic distillation and then the solvent composition adjusted to give an ethyl acetate/IMS mixture (15 vol., 60:1 ratio). The solution was then warmed to approx. 70°C. p-toluene sulphonic acid monohydrate (1.1 eq.) was added and stirred at approx. 70°C, the resultant solution was then cooled to approx. 30-40°C. Authentic N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (tosylate salt) was then introduced as a seed and the solution aged below 25°C. The solid was isolated by filtration, may be washed with EtOAc (2 x 2vol.) and then dried *in vacuo* at 45-55°C.

Typical yield 70-75%th

^{1}H NMR (DMSO-d_6, 500 MHz) ppm 13.14 (s, 1H, 1NH^+), 8.65 (d, 1H, 7NH), 8.23 (d, 1H, 2), 8.09 (d, 1H, 6), 7.53 (d, 2H, 29,31), 7.11 (d, 2H, 28,32), 7.03 (dd, 1H, 3), 6.91 (dd, 1H, 5), 6.78 (s, 1H, 13), 6.69 (s, 1H, 15), 6.61 (s, 1H, 17), 4.40 (bs, -, rotamer of 21), 4.22 (m, 1H, 8), 4.08 (dd, 1H, 10), 3.98 (dd, 1H, 10'), 3.77 (bs, 1H, 21), 3.46 (s, -, water), 3.28,3.12(2bs, 2H, 24), 2.50 (p, -, dmso-d_5), 2.28, 2.27 (2s, 6H, 18,26), 1.34-0.82 (bm, 9H, 22,23,25), 1.27 (d, 3H, 9).

(iii) Method 3

Diethyl carbonate (0.96 vol., 0.93 wt., 1.2 mol. eq) is added to a pre-formed suspension of (S)-2-(Pyridin-4-ylamino)-propan-1-ol (1wt.,1mol.eq.) (Intermediate 1 prepared as described above or as described in WO97/22589

and WO00/20394), caesium carbonate (3.2 wt., 1.5 mol. eq.) and N-ethyl-3-hydroxy-N-isopropyl-5-methylbenzamide (1.6 wt., 1.1 mol. eq.) in NMP (5.0 vol.) at approx.110°C.

The resultant suspension is then heated to approx. 130°C and maintained for at least 18 hours.The contents are cooled and diluted with water (8.0 vol.) and MIBK (3.0 vol.).

The layers are separated and the aqueous layer backwashed with MIBK (2.0 vol.). The organic layers are combined and washed with 2M NaOH (5.0 vol.) then water (2 x 5.0vol.). The layers are separated and the product containing organic layer retained.

N-ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (1.0 wt, 1.0 mol. eq.) in MIBK (3-3.5vol.) is heated to approx. 50°C. p-Toluene sulfonic acid monohydrate (1.0 mol. eq., 0.54 wt.) pre dissolved in MIBK (7 vol.) is then charged and the contents maintained at 50-55°C.

The resultant solution is then concentrated by vacuum distillation, 5.0 vol. of MIBK are removed and cooled to approx. 22°C over 3 hours, seeded with authentic N-ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (tosylate salt) and aged for about 18 hours.

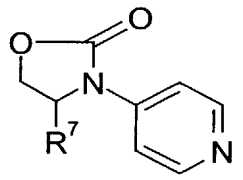
The solid is isolated by filtration, washed with MIBK (2 x 3.0 vol.) and dried *in vacuo* at approx. 60°C to afford N-ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide (tosylate salt) as a white solid.

Typical yield = 75-80%th

^{1}H NMR (DMSO-d_6, 500 MHz) ppm 13.14 (s, 1H, 1NH$^+$), 8.65 (d, 1H, 7NH), 8.23 (d, 1H, 2), 8.09 (d, 1H, 6), 7.53 (d, 2H, 29,31), 7.11 (d, 2H, 28,32), 7.03 (dd, 1H, 3), 6.91 (dd, 1H, 5), 6.78 (s, 1H, 13), 6.69 (s, 1H, 15), 6.61 (s, 1H, 17), 4.40 (bs, -, rotamer of 21), 4.22 (m, 1H, 8), 4.08 (dd, 1H, 10), 3.98 (dd, 1H, 10'), 3.77 (bs, 1H, 21), 3.46 (s, -, water), 3.28,3.12(2bs, 2H, 24), 2.50 (p, -, dmso-d_5), 2.28, 2.27 (2s, 6H, 18,26), 1.34-0.82 (bm, 9H, 22,23,25), 1.27 (d, 3H, 9).

Claims:

1. A compound of formula (II) or a pharmaceutically acceptable salt or solvate thereof:

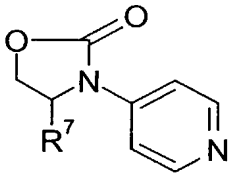


(II)

wherein:

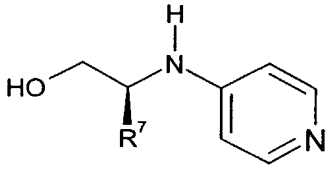
R^7 represents hydrogen or C_{1-6}alkyl.

2. A process for the preparation of a compound of formula (II):



(II)

by cyclisation of a compound of formula (IV):

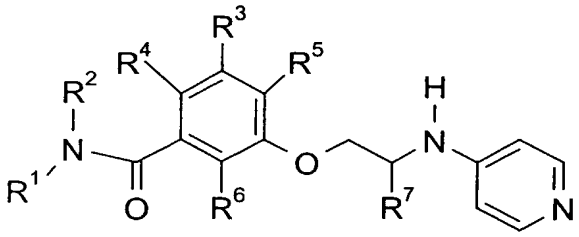


(IV)

wherein:

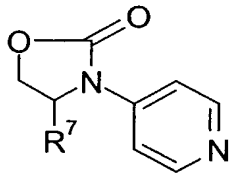
R^7 represents hydrogen or C_{1-6}alkyl.

3. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

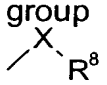
comprising the step of preparing a compound of formula (II) or a pharmaceutically acceptable salt or solvate thereof:



(II)

wherein:

R^1 and R^2 independently represent a group



or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

R^7 represents hydrogen or C_{1-6}alkyl;

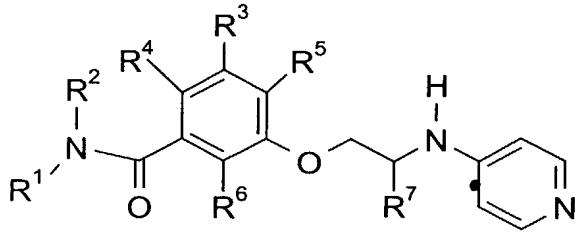
R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally

substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

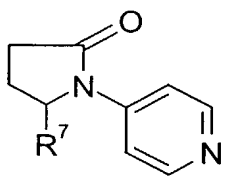
R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl.

4. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:

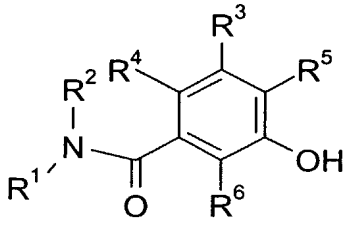


(I)

comprising the step of reacting a compound of formula (II) with a compound of formula (III):

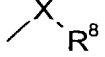


(II)



(III)

wherein:

R^1 and R^2 independently represent a group 

or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

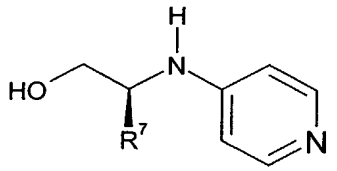
R^7 represents hydrogen or C_{1-6}alkyl;

R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

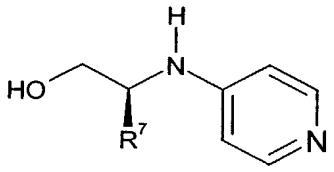
R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl.

5. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claim 3 or 4 wherein the compound of formula (II) is prepared by cyclisation of a compound of formula (IV):



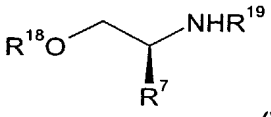
(IV)

6. A process for the preparation of a compound of formula (IV):

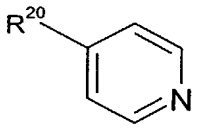


(IV)

comprising reacting a compound of formula (V) with a compound of formula (VI):



(V)

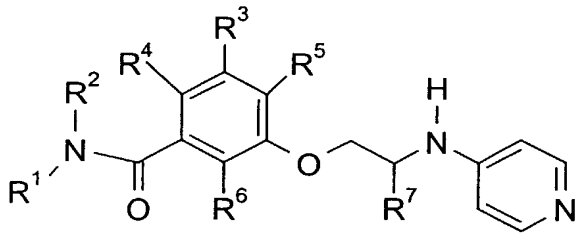


(VI)

wherein:

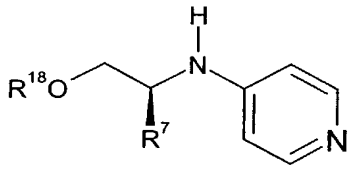
R^7 represents hydrogen or C_{1-6}alkyl;
R^{18} represents hydrogen, or a suitable oxygen protecting group;
R^{19} represents hydrogen, or a suitable amino protecting group; and
R^{20} represents halogen.

7. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



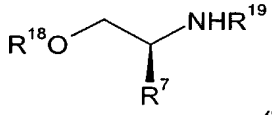
(I)

comprising the step of preparing a compound of formula (IV) or a pharmaceutically acceptable salt or solvate thereof:

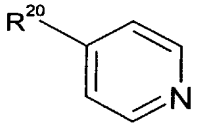


(IV)

by reacting a compound of formula (V) with a compound of formula (VI):



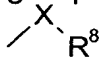
(V)



(VI)

wherein:

R^1 and R^2 independently represent a group



or R^1 and R^2 together form a C_{3-7}heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6}alkyl, C_{1-4}alkoxy, halogen, carboxylic acid or a C_{1-4}carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3}alkyl, halogen, or C_{1-2}alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

R^7 represents hydrogen or C_{1-6}alkyl;

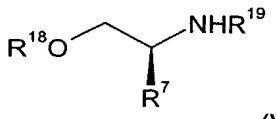
R^8 represents hydrogen, C_{3-8}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-7}heterocycloalkyl, C_{3-7}heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6}alkyl chain, or a C_{3-6}alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

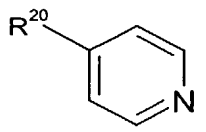
R^9-R^{17} represent hydrogen, C_{1-6}alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl;

R^{18} represents hydrogen, or a suitable oxygen protecting group;
R^{19} represents hydrogen, or a suitable amino protecting group; and
R^{20} represents halogen.

8. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claim 5 wherein the compound of formula (IV) is prepared by reacting a compound of formula (V) with a compound of formula (VI):



(V)



(VI)

wherein:

R^7 represents hydrogen or C_{1-6}alkyl;
R^{18} represents hydrogen, or a suitable oxygen protecting group;
R^{19} represents hydrogen, or a suitable amino protecting group; and
R^{20} represents halogen.

9. A process as claimed in any one of claims 3, 4, 5, 7 or 8 wherein the compound of formula (I) is N-Ethyl-N-isopropyl-3-methyl-5-[2S-(pyridin-4-ylamino)-propoxy]-benzamide.

10. A process as claimed in any one of claims 2, 5, 6, 7 or 8 wherein the compound of formula (IV) is (S)-2-(Pyridin-4-ylamino)-propan-1-ol.

INTERNATIONAL SEARCH REPORT

Inte _ onal Application No
PCT/GB 02/03185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/04 C07D213/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 22589 A (GLAXO GROUP LTD; WATSON NIGEL STEPHEN (GB); PASS MARTIN (GB); PATE) 26 June 1997 (1997-06-26) cited in the application Pages 19-22, process A; and pages 22-23, process B for compounds (I). ---	1-5,8-10
A	WO 00 20394 A (PASS MARTIN; GLAXO GROUP LTD (GB); KELLY HENRY ANDERSON (GB); SMIT) 13 April 2000 (2000-04-13) cited in the application Pages 9-10, processes A-D for compounds (I); pages 17-19, intermediates 1,2,6; page 22, example 1; page 25, last paragraph, example 12. --- -/--	1-5,8-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2002	06. 11. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/03185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 8 (all complete) and 9-10 (part)

   directed to compounds (II), a process for preparing compounds (II), and a process for preparing compounds (I) involving compounds (II),

2. Claims: 6-7 (complete) and 9-10 (part)

   directed to a process for preparing compounds (IV) and a process for preparing compounds (I) comprising the step of preparing compounds (IV).

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Foerderung der chemischen Wissenschaften, Frankfurt am Main, DE; XP002212037 Database Accsession no. 139712 (BRN): reactions 6,9,10,20-23. & J. PRAKT. CHEM., vol. 2, no. 44, 1891, page 18 ---	1-5,8-10
A	FANCHER, L. W. ET AL.: "Anomalous ring opening of N-aryl-2-oxazolidinones ..." TETRAHEDRON LETT., vol. 29, no. 40, 1988, pages 5095-5098, XP002212036 the whole document ---	4,5,8-10
A	VON DER SAAL, W. ET AL.: "Derivatives of 4-amino-pyridine as selective thrombin inhibitors" BIOORG. MED. CHEM. LETT., vol. 7, no. 10, 1997, pages 1283-1288, XP002914979 Page 1284, compound 4. ---	6
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Foerderung der chemischen Wissenschaften, Frankfurt am Main, DE; XP002217100	6
Y	Database Accession no. 3943150 (Reaction ID). & J. MED. CHEM., vol. 37, no. 23, 1994, pages 3977-3985, ---	7,9,10
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Foerderung der chemischen Wissenschaften, Frankfurt am Main, DE; XP002217101	6
Y	Database Accession no. 32613 (Reaction ID). & J. ORG. CHEM., vol. 14, 1949, page 868 ---	7,9,10

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Foerderung der chemischen Wissenschaften, Frankfurt am Main, DE; XP002217102	6
Y	Database Accession no. 32457 (Reaction ID). & JUSTUS LIEBIGS ANN. CHEM., vol. 521, 1936, page 286	7,9,10

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 02/03185

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		NO 20011654 A	30-05-2001
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		US 6441008 B1	27-08-2002